

University of Groningen

Patient Selection for Bronchoscopic Lung Volume Reduction

Welling, Jorrit B A; Hartman, Jorine E; Augustijn, Sonja W S; Kerstjens, Huib A M; Vanfleteren, Lowie E G W; Klooster, Karin; Slebos, Dirk-Jan

Published in:
International Journal of Chronic Obstructive Pulmonary Disease

DOI:
[10.2147/COPD.S240848](https://doi.org/10.2147/COPD.S240848)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Welling, J. B. A., Hartman, J. E., Augustijn, S. W. S., Kerstjens, H. A. M., Vanfleteren, L. E. G. W., Klooster, K., & Slebos, D-J. (2020). Patient Selection for Bronchoscopic Lung Volume Reduction. *International Journal of Chronic Obstructive Pulmonary Disease*, 15, 871-881. <https://doi.org/10.2147/COPD.S240848>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.



ORIGINAL RESEARCH

Patient Selection for Bronchoscopic Lung Volume Reduction

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease

Jorrit BA Welling ^{1,2}
Jorine E Hartman ^{1,2}
Sonja WS Augustijn¹
Huib AM Kerstjens ^{1,2}
Lowie EGW Vanfleteren³
Karin Klooster^{1,2}
Dirk-Jan Slebos^{1,2}

¹University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases, Groningen, the Netherlands; ²Groningen Research Institute for Asthma and COPD, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; ³COPD Center, Sahlgrenska University Medical Hospital and Institute of Medicine, Gothenburg University, Gothenburg, Sweden

Purpose: Bronchoscopic lung volume reduction (BLVR) is a valuable treatment option for carefully selected patients with severe COPD. There is limited knowledge about the characteristics and outcomes of patients referred to a specialized center for BLVR. The study objectives were to investigate the selection rate for BLVR treatment in patients referred for this treatment and to investigate the differences between patients that were selected for BLVR and patients that were not.

Patients and Methods: We performed a retrospective analysis of patients with severe COPD who were referred to our hospital to assess eligibility for BLVR treatment. Our parameters included demographics, comorbidity, chest computed tomography characteristics, reasons for rejection from BLVR treatment and patient survival.

Results: In total, 1500 patients were included (mean age 62 years, 50% female and forced expiratory volume in 1 s 33% of predicted). Out of this group, 282 (19%) patients were selected for BLVR treatment. The absence of a suitable target lobe for treatment, an unsuitable disease phenotype and insufficient lung hyperinflation were the most important factors for not being selected. Patients that were selected for any BLVR option lived significantly longer than the group of patients that were not selected for BLVR (median 3060 versus 2079 days, $P < 0.001$).

Conclusion: We found that only a small proportion of patients that are referred for BLVR treatment is eligible for a BLVR treatment, indicating a need for both better referral tools and for the development of new therapies for this group of patients. Furthermore, our data suggest that selection for BLVR is associated with a significant survival benefit.

Keywords: bronchoscopic lung volume reduction, patient selection, endobronchial valves, lung volume reduction coils

Introduction

Bronchoscopic lung volume reduction (BLVR) is a valuable treatment option for patients with severe COPD and emphysema, aimed at reducing hyperinflation of the lung.¹ BLVR using endobronchial valves (EBV) and lung volume reduction coils (LVRC) have been studied most extensively and demonstrated to be effective, with an acceptable safety profile.²

Dedicated patient selection for BLVR is essential in achieving clinically meaningful results after treatment. For example, for the EBV treatment, the absence of interlobar collateral ventilation is necessary to achieve successful outcomes and for the LVRC treatment superior outcomes are observed in patients with very severe static hyperinflation and absence of significant airway disease.^{3–7}

Several questions on patient selection for BLVR remain unanswered. For example, it is unknown what proportion of patients referred for BLVR is potentially eligible for

Correspondence: Jorrit BA Welling
Department of Pulmonary Diseases,
University Medical Center Groningen,
Groningen, the Netherlands
Email j.b.a.welling@umcg.nl



any form of BLVR treatment and to our knowledge, this group of patients has not been well characterized in the literature. Furthermore, the development of new insights in BLVR treatment during this period led to changes in the inclusion and exclusion criteria for these treatments which potentially could influence the proportion of selected patients.

Therefore, we aimed to investigate 1) which proportion of patients that were referred to our hospital were actually selected for BLVR treatment; 2) the differences in characteristics and survival between patients that were and were not selected for BLVR; 3) to what extent applying updated criteria for eligibility would have affected the selection rate.

Patients and Methods

Study Design and Patient Population

We performed a retrospective analysis of the first 1500 patients who were consecutively referred to assess eligibility for BLVR treatment between March 2007 and October 2014, from 62 different hospitals in the Netherlands to our hospital. Given the retrospective and anonymous nature of the analyses, this research did not fall within the scope of the WMO (Dutch Medical Research with Human Subjects Law) and therefore review by a medical ethical committee was not required.

Evaluation of Eligibility

Patient selection for BLVR in our hospital starts with the referral of a patient by their pulmonary physician. Referring physicians are requested to include recent lung function results (spirometry and body plethysmography), chest computed tomography (HRCT) scan, and a complete medical history in their referrals. During a multidisciplinary team meeting, a first selection is made. Potential BLVR

candidates are invited to our hospital for a consultation with an interventional pulmonologist.

Treatment

Patients that were eligible for BLVR treatment were included in clinical trials investigating EBV,^{3,8–11} LVRC,^{12–15} polymeric lung volume reduction,¹⁶ pneumostoma^{17–19} and airway bypass stents²⁰ or in our regular EBV treatment program (BREATH-NL: NCT02815683).

Outcomes

The primary outcome of this study was the selection rate for BLVR treatment. Secondary outcomes were derived from the referral documentation and included demographics, lung function (spirometry and body plethysmography), smoking status, oxygen therapy use and maintenance anticoagulant use. Furthermore, the medical history of all patients was screened for a selection of comorbidities. All available CT scans were visually reviewed and assessed by JBAW for the presence of specific characteristics, these assessments were supervised by DJS.

The degree of emphysema destruction was scored on a 0 to 4 qualitative Likert scale with higher scores indicating more emphysematous destruction (Figure 1).^{21,22} In case of ineligibility for BLVR, we reported the reasons why patients were found not to be eligible for treatment. The survival status of the referred patients was verified with the Dutch government (Personal Records Database) on June 16, 2019.

Theoretical Model

We applied some of the most recent inclusion and exclusion criteria for EBV and LVRC, according to the guidelines,¹ on our cohort to assess the proportion of patients eligible for these treatments and whether this

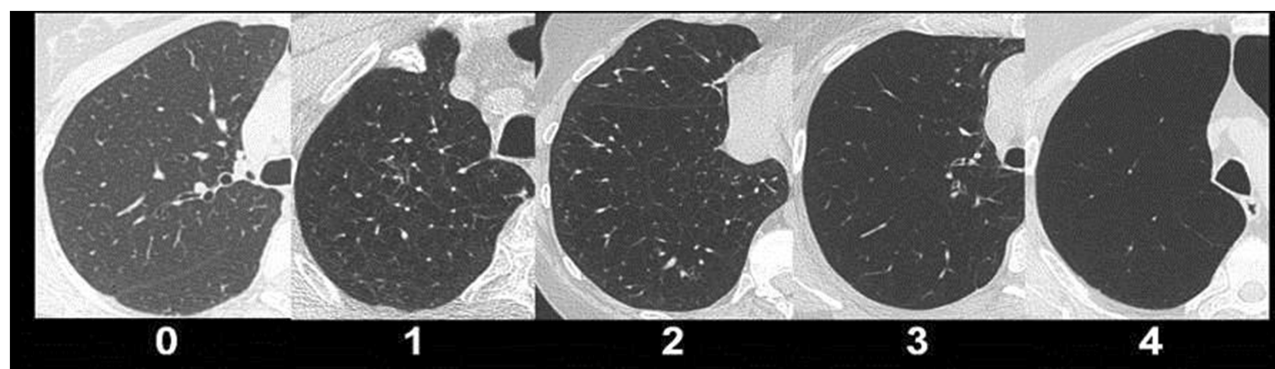


Figure 1 Qualitative scale of emphysematous destruction, scored on a 0 to 4 scale with higher scores indicating more emphysematous destruction.

proportion was different from the proportion of patients actually selected for these treatments. The criteria applied for EBV treatment included forced expiratory volume in 1 s (FEV₁) between 20% and 50% of predicted, residual volume (RV) $\geq 175\%$ of predicted, RV/total lung capacity (TLC) ratio of ≥ 0.58 , visually intact major fissure (left or right) and emphysema destruction ≥ 2 on destruction scale (Figure 1).

The criteria applied for LVRC included FEV₁ between 20% and 50% of predicted, RV $\geq 200\%$ of predicted, RV/TLC ratio of ≥ 0.58 and emphysema destruction ≥ 2 on the destruction scale (Figure 1).

Statistical Analysis

Differences in patient characteristics between the group that was selected for treatment and the group that was not were analyzed using an independent-samples *T*-test in case of normal distribution of data and a Mann–Whitney–*U* test in case of non-normal distribution. A Chi-squared test was used in the case of categorical data. Due to the explorative nature of the CT data, only demographic data are presented and no statistical analysis was performed. Survival time was defined as the time after the date of discussion in the multidisciplinary team meeting until the date of verification with the Dutch government. Survival was analyzed using the Kaplan–Meier method. Comparison in survival between the groups selected or not selected for treatment was performed using the Mantel–Cox log-rank test and comparison in survival between EBV and LVRC treatment was performed using Breslow's test. All statistical analyses were performed using SPSS version 23 (IBM, New York, NY, USA). *P*-values < 0.05 were considered statistically significant.

Results

In total, 1500 patients (50% female) were included in our analysis, with a mean age of 62 years and FEV₁ of $33 \pm 14\%$ of predicted (additional patient characteristics are shown in Table 1). From this group, 651 patients (43%) were invited for a consultation in our hospital. Of the total referred population 282 (19%) patients were selected for a clinical trial or regular treatment program and therefore a total of 1218 (81%) patients were considered not eligible for BLVR (see Figure 2 for patient flowchart).

Out of the group of 282 patients that were selected for a bronchoscopic treatment, 175 patients (62%) were selected for EBV, 93 patients (33%) for LVRC, 3 patients (0.2%) for airway bypass stents, 9 patients (3%) for

polymeric lung volume reduction and 2 patients (0.1%) for a pneumostoma.

Patients selected for BLVR were significantly younger (59 versus 63 years), had a lower FEV₁ (28% versus 34% of predicted) and a higher RV (237% versus 215% of predicted) compared to the group of patients not selected for BLVR (all $P < 0.001$).

The most frequently encountered reasons for ineligibility for BLVR treatment were: absence of a suitable target lobe for treatment (18%), unsuitable disease phenotype for treatment (chronic bronchitis, frequent exacerbations, asthma) (18%) and insufficient hyperinflation of the lungs (16%). See Table 2 for the complete list of contraindications.

The CT scans of 1211 patients (81%) could be assessed, for 289 patients assessment was not possible because of scan unavailability or insufficient image quality for assessment. The proportion of patients with a homogeneous and heterogeneous distribution of emphysema was similar (52% versus 48%). Upper lobe predominant emphysema was observed more often than lower lobe predominant emphysema (71% versus 29%). The left major fissure was found to be visually intact in 44% of patients, the right major in 25% of patients and the right minor fissure in 12% of patients (see Table 3).

Table 4 displays the reported comorbidities. Patients referred for BLVR had an average of 1.4 comorbidities and the most frequently encountered comorbidities were hypertension (22%), confirmed or suspected asthma (18%) and coronary artery disease (10%). Patients selected for BLVR had significantly less comorbidities compared to the group of patients not selected for BLVR (1.1 versus 1.4, $P < 0.01$).

The survival status of 1272 patients (85%) could be verified. The overall median survival was 2316 days (95% CI: 2146–2485 days). The median follow-up was 2351 days (95% CI: 2451–2514 days). Patients that were referred to our hospital but were not invited for consultation had a median survival of 1808 days (95% CI: 1622–1994) and patients who were invited for consultation but who were not selected for treatment had a median survival of 2524 days (95% CI: 2234–2814). Patients that were selected for BLVR lived significantly longer than the group of patients that was not selected for BLVR (median 3060 versus 2079 days, $P < 0.001$), see Figure 3. No significant survival difference was observed between patients who were selected for EBV treatment and those who were selected for LVRC ($P = 0.45$).

Table 1 Patient Characteristics

	All Referrals	Selected for Treatment	Not Selected for Treatment	P value
Number of patients	1500	282	1218	
Age (years)	62±9	59±8	63±9	P<0.001
Female	750 (50%)	179 (63%)	571 (47%)	P<0.001
BMI (kg/m ²)	24±5	24±4	24±5	P=0.02
Pack-years (years)	38±18	36±16	38±18	P=0.18
FEV ₁ (L)	0.9±0.5	0.8±0.3	1.0±0.5	P<0.001
FEV ₁ predicted (%)	33±14	28±8	34±15	P<0.001
FVC (L)	2.8±1.0	2.6±0.9	2.8±1.0	P=0.01
FVC predicted (%)	79±21	77±19	79±22	P=0.08
RV (L)	4.8±1.3	4.9±1.1	4.7±1.3	P=0.03
RV predicted (%)	219±56	237±46	215±58	P<0.001
TLC (L)	7.8±1.6	7.8±1.5	7.8±1.6	P=0.77
TLC predicted (%)	130±18	135±15	129±19	P<0.001
Current smoker	123 (8%)	10 (4%)	113 (9%)	P<0.01
Ex-smoker	1051 (70%)	263 (94%)	788 (65%)	P<0.001
Never smoker	16 (1%)	2 (1%)	14 (1%)	P=0.52
Unknown	302 (20%)	6 (2%)	296 (24%)	P<0.001
Oxygen therapy	418 (28%)	80 (28%)	338 (28%)	P=0.84
Maintenance anticoagulant use	280 (19%)	44 (16%)	236 (19%)	P=0.14
Participation in previous pulmonary rehabilitation or weekly physiotherapy	684 (46%)	174 (62%)	510 (42%)	P<0.001
Weekly physiotherapy	567 (38%)	168 (60%)	399 (33%)	P<0.001

Notes: Data are presented as the number of patients (%), mean ± standard deviation or percentage of the predicted value ± standard deviation. Differences in patient characteristics between the selected and not selected group for treatment were analyzed using a 2-samples T-test or Chi-square test.

Abbreviations: BMI, body mass index; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity.

Theoretical Model

When applying some of the currently established inclusion and exclusion criteria for endobronchial valve treatment and lung volume reduction treatment, we identified 283 patients eligible for EBV treatment (19%) while 175 patients (12%) were actually selected for EBV in this cohort and 144 patients (10%) would currently be eligible for LVRC while 93 patients (6%) were actually selected for LVRC (Figure 4).

Discussion

Only one out of five patients who were referred for BLVR treatment to our hospital were selected for BLVR treatment. Ineligibility for BLVR treatment was most often caused by the absence of a suitable target lobe for treatment, an unsuitable disease phenotype for treatment and insufficient lung hyperinflation. Overall survival in the group of patients referred for BLVR was poor with a median survival of approximately 6 years.

To our knowledge, this is the largest study investigating patients referred for BLVR eligibility assessment. In

a recent study by Polke et al, who studied patients that were referred to a BLVR expert center in Heidelberg (Germany), a higher proportion of patients were found to be eligible for BLVR treatment, possibly caused by a more strict preselection of patients for referral.²³ The same study also found the absence of a suitable target lobe to be the most frequent contra-indication for BLVR, which is in line with the results of our study.²³

Only a small proportion of the already preselected group of patients that were considered to be eligible for BLVR by the referring physician is selected for BLVR treatment. This highlights both the need for improved referral strategies on the one hand and the important need for additional therapeutic options for patients with severe COPD on the other hand. Alternative interventions for BLVR include lung volume reduction surgery or lung transplantation; however, both treatments suffer from huge limitations related to the invasiveness of the procedure, scarce availability and strict selection procedures. Patients with a severe chronic bronchitis phenotype of COPD are a common example of an unsuitable disease phenotype for BLVR. Both endobronchial treatment with liquid nitrogen

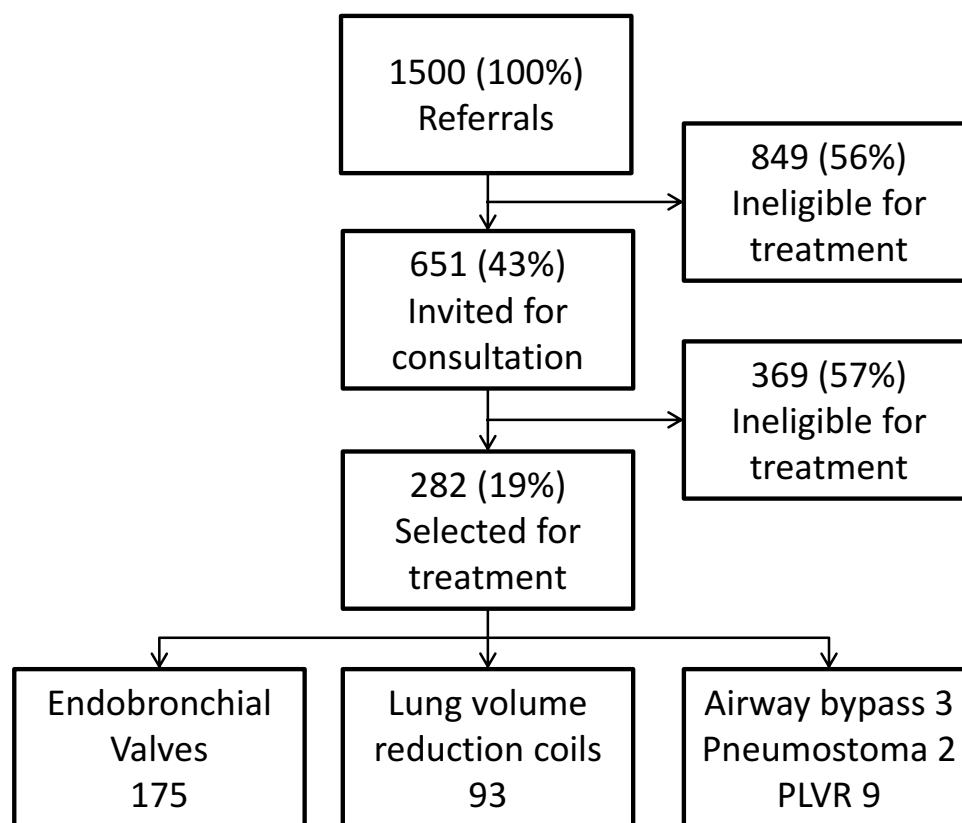


Figure 2 Study flowchart.

Abbreviation: PLVR, polymeric lung volume reduction.

cryospray and targeted lung denervation are currently under development for this phenotype. Liquid nitrogen cryospray is a treatment aimed at inducing an airway tissue healing effect by destroying the hyperplastic goblet cells and excess submucous glands.²⁴ Target lung denervation is a treatment designed to decrease airway resistance and mucus hyper secretion, by inhibiting parasympathetic pulmonary nerves, using radiofrequency ablation therapy.²⁵

New insights into BLVR treatment caused inclusion and exclusion criteria for these treatments to change over time, which might have affected the proportion of patients considered eligible for BLVR. For example, a previous contra-indication for EBV trials included the presence of alpha-1 antitrypsin deficiency, but these patients are now considered eligible for treatment.^{3,26} When we applied the most recent inclusion and exclusion criteria on our cohort, we observed a discrepancy between the number of patients that were eligible for treatment and those who were actually selected for treatment. This could be the result of the fact that not all treatments were available at all times during the time frame of this study, the clinical trial

context with strict in and exclusion criteria or because we applied only a selection of the most stringent criteria in our model.

A significant survival benefit was observed for the group of patients that was selected for BLVR treatment, when compared to the group that was not selected for treatment. This survival benefit was already observed in several previous studies which demonstrated that when successful lobar atelectasis is achieved after EBV treatment, patients have a substantial, persisting survival benefit.^{27–29} Structural survival data for the LVRC treatment are not yet available. We acknowledge that the survival benefit observed in the group of patients that were selected for treatment might have not only been due to a direct result of the actual intervention but also caused by the exclusion of patients that were too frail, due to any cause, for treatment. On the other hand, both the degree of hyperinflation and airway obstruction were higher in the group selected for treatment, suggesting the selection of patients with severe disease for treatment. In addition, given that most treatments in this cohort took place in the early phase of the development of these treatments,

Table 2 Contraindications in Patients Not Selected for BLVR

Contraindication	Prevalence
Number of patients	1218
Number of contraindications	
Mean \pm standard deviation	1.3 \pm 0.9
Median (range)	1 (0–5)
Absence of suitable target lobe for treatment	221 (18%)
Unsuitable disease phenotype (chronic bronchitis, frequent exacerbations, asthma)	219 (18%)
Insufficient hyperinflation of the lungs	197 (16%)
Presence of comorbidity	162 (13%)
Homogeneous distribution of emphysema	125 (10%)
Incomplete interlobar fissures	109 (9%)
Patient renounced treatment	95 (8%)
Pulmonary function testing outcomes not meeting minimum hyperinflation and/or airway obstruction requirements	95 (8%)
No trial available at moment of evaluation	94 (8%)
Low degree of emphysema destruction	83 (7%)
Did not stop smoking for >6 months	79 (7%)
Did not yet participate in pulmonary rehabilitation	73 (6%)
Maintenance anticoagulant use	54 (5%)
Too high degree of emphysema destruction	53 (4%)
Presence of bullae	47 (4%)
Paraseptal emphysema phenotype	47 (4%)
High level of exercise capacity	43 (4%)
Suspicious nodules in the lung that require follow-up	38 (3%)
Too poor condition for treatment	35 (3%)
Prior thoracic surgery	31 (3%)
Body mass index too high or too low	26 (2%)
Pulmonary Hypertension	22 (2%)
Alpha-1 antitrypsin deficiency	15 (1%)
Lung transplanted before BLVR treatment	3 (0.2%)

Notes: Data are presented as number of contraindications (percentage of patients with contraindication), mean \pm standard deviation, median (range).

Abbreviation: BLVR, bronchoscopic lung volume reduction.

the current data might actually underestimate the survival benefit of these treatments.

Patients selected for BLVR had significantly less comorbidities than patients who were not selected for BLVR. On average, the referred patients had more than one comorbidity. However, this was still lower than in a study by Putcha et al, possibly caused by the underreporting of comorbidities by the referring physicians in our cohort or because of the fact that the referring physicians already referred a preselected population due to study selection criteria on comorbidity.^{30,31}

We assessed the CT characteristics of the referred patients and found the left major fissure to be most often intact on the CT scans of the referred patients, followed by the right major fissure and the right minor fissure. The proportion of visually intact fissures was in line with

Table 3 CT Characteristics

	All Referrals	Selected for Treatment	Not Selected for Treatment
Number of patients	1500	282	1218
Scans available	1211	274	937
Mild centrilobular	428 (35%)	80 (29%)	348 (37%)
Severe centrilobular	440 (36%)	113 (41%)	327 (35%)
Panlobular	189 (16%)	66 (24%)	123 (13%)
Paraseptal	146 (12%)	15 (6%)	131 (14%)
No emphysema	8 (0.7%)	0 (0%)	8 (1%)
Distribution homogeneous/heterogeneous (%)	48/52	31/69	53/47
Upper/Lower lobes predominant (%)	71/29	64/36	75/25
Destruction LUL 1/2/3/4 (%)	40/38/19/2	35/46/19/1	42/35/19/3
Destruction LLL 1/2/3/4 (%)	55/31/11/1	52/33/13/2	56/31/10/1
Destruction RUL 1/2/3/4 (%)	37/35/24/3	33/39/26/2	38/34/23/3
Destruction RLL 1/2/3/4 (%)	56/32/10/1	53/32/13/2	56/31/9/1
Left major fissure (intact/>90%intact/<90%intact/unknown (%))	44/26/29/2	58/20/22/0	40/28/31/2
Right major fissure (intact/>90% intact/<90% intact/unknown (%))	25/32/41/1	36/31/33/0	22/33/44/2
Right minor fissure (intact/>90% intact/<90% intact/unknown (%))	12/14/72/3	12/18/70/0	11/13/72/3
Bronchopathy	666 (55%)	140 (51%)	526 (56%)
Mild bronchiectasis	151 (13%)	30 (11%)	121 (13%)
Severe bronchiectasis	20 (2%)	1 (0.4%)	19 (2%)
Giant bullae	195 (16%)	21 (8%)	174 (19%)
Nodules requiring follow up	89 (7%)	27 (10%)	62 (7%)
Fibrosis	23 (2%)	2 (0.7%)	21 (2%)
Pleural pathology	13 (1%)	2 (0.7%)	11 (1%)

(Continued)

Table 3 (Continued).

	All Referrals	Selected for Treatment	Not Selected for Treatment
Suspect for pulmonary hypertension	148 (12%)	25 (9%)	123 (13%)

Notes: Data is presented as number of patients (percentage of patients) or as percentage of cases. Destruction score based on a 1 to 4 Likert scale, with higher scores indicating more severe emphysematous destruction.

Abbreviations: CT, computed tomography; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RLL, right lower lobe.

previously published data on this topic, and also in agreement with the latest clinical trials investigating EBV and intrabronchial valves, in which the left upper and left lower lobe were selected for treatment in more than 75% of cases.^{11,32,33}

This study has several limitations: first of all, our population is representative of the group of patients referred to a BLVR center but not of the total population of patients with severe emphysema, and can therefore not serve to accurately assess the proportion of eligible patients for BLVR in the total population of patients with emphysema. Second, inherent to the retrospective nature of this study, we had to rely on the quality of the referral documentation from other hospitals. Incomplete or incorrect referral documentation might have especially affected the data presented on comorbidity, which was based on the medical history included in the referral documentation, probably leading to an underestimation of comorbidity.³¹ Third, the CT scans were of very different quality and settings, because referral material was used, making a preferred quantitative assessment not possible.³⁴ These scans were assessed by one reviewer only (JBAW), under supervision of one of the authors (DJS), a task that in an ideal setting would have been performed by a panel of reviewers. Fourth, since these were the first 1500 BLVR referrals sent to our hospital, most patients were treated in a clinical trial context, which probably led to a more strict selection compared to treatment outside the clinical trial context, underestimating the number of patients eligible for BLVR treatment. Fifth, it would have been of additional value to include a survival prediction index like BODE, but we did not have the necessary data available to perform this.³⁵

Table 4 Comorbidities Reported in the Referral Documentation

Comorbidity	All Referrals	Selected for Treatment	Not Selected for Treatment
Number of patients	1500	282	1218
Number of comorbidities* mean±standard deviation median (range)	1.4±1.4 1 (0–11)	1.1±1.2 1 (0–6)	1.4±1.5 1 (0–11)
Hypertension	323 (22%)	72 (26%)	251 (21%)
Confirmed or suspected asthma	270 (18%)	58 (21%)	212 (17%)
Coronary artery disease	153 (10%)	16 (6%)	137 (11%)
Dyslipidemia	117 (8%)	20 (7%)	97 (8%)
Diabetes	112 (8%)	15 (5%)	97 (8%)
Osteoporosis	105 (7%)	19 (7%)	86 (7%)
Obesity (BMI>30)	105 (7%)	12 (4%)	93 (8%)
Atrial fibrillation	84 (6%)	4 (1%)	80 (7%)
Myocardial infarction	82 (6%)	6 (2%)	76 (6%)
Cerebrovascular incident	76 (5%)	12 (4%)	64 (5%)
Alpha-1 antitrypsin deficiency	70 (5%)	16 (6%)	54 (4%)
Peripheral artery disease	59 (4%)	6 (2%)	53 (4%)
Heart failure	54 (4%)	5 (2%)	49 (4%)
Depression	54 (4%)	11 (4%)	43 (4%)
Pulmonary embolus	48 (3%)	10 (4%)	38 (3%)
Pulmonary hypertension	46 (3%)	1 (0.4%)	45 (4%)
Gastro-oesophageal reflux disease	43 (3%)	7 (3%)	36 (3%)
Degenerative joint disease	38 (3%)	4 (1%)	34 (3%)
Anxiety	35 (2%)	7 (3%)	28 (2%)

(Continued)

Table 4 (Continued).

Comorbidity	All Referrals	Selected for Treatment	Not Selected for Treatment
Obstructive sleep apnea syndrome	33 (2%)	5 (2%)	28 (2%)
Gastric ulcer	24 (2%)	2 (1%)	22 (2%)
Pulmonary malignancy	21 (1%)	2 (1%)	19 (2%)
Anemia	20 (1%)	0 (0%)	20 (2%)
Chronic kidney disease	15 (1%)	0 (0%)	15 (1%)
Pulmonary fibrosis	10 (0.7%)	0 (0%)	10 (0.8%)
Liver cirrhosis	2 (0.1%)	1 (0.4%)	1 (0.1%)

Notes: Data are presented as the number of patients (percentage of patients), mean \pm standard deviation or median (range). Differences in the number of comorbidities were assessed using Mann–Whitney U-test. * $P < 0.01$.

Abbreviation: BMI, body mass index.

A strength of our study is the large number of patients that were included in this retrospective study. Another strength of our study is the fact that we were able to verify the survival status of our patients with the Dutch government, which increased the reliability of our survival data.

Future research might include the development of a model that is able to predict the *a priori* chances of BLVR eligibility. Such a model could assist both physicians and patients in deciding whether referral to

a BLVR center is indicated. Indeed, the right patient should be referred for the right treatment, to improve efficiency and avoid the burden for the patient. Future research is needed to identify the size of the potential pool of patients eligible for BLVR treatment as a previous study by Pietzsch et al suggested that BLVR currently is only used in a small proportion of patients with severe emphysema.³⁶

In conclusion, we found that only a small proportion of patients that are referred for BLVR treatment is eligible for a BLVR treatment, indicating a need for the development of new therapies for this group of patients and better referral tools. Furthermore, our data suggest that selection for BLVR is associated with a significant survival benefit.

Abbreviations

BLVR, bronchoscopic lung volume reduction; COPD, chronic obstructive pulmonary disease; CT, computed tomography; EBV, endobronchial valves; FEV₁, forced expiratory volume in 1 s; LVRC, lung volume reduction coil; RV, residual volume; TLC, total lung capacity.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

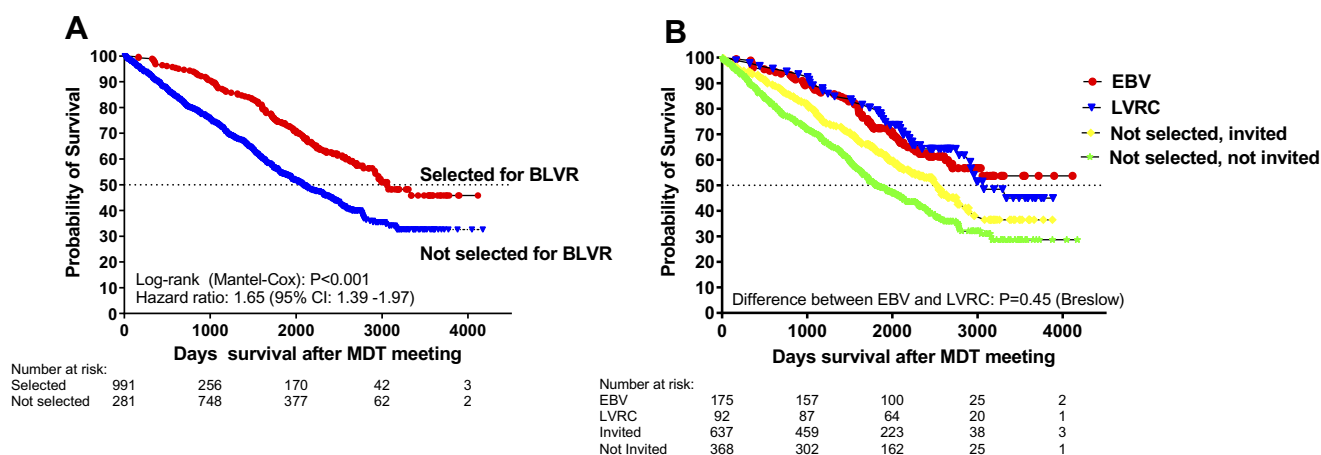


Figure 3 Kaplan-Meier plots of survival. (A) Survival of the patients that were selected for treatment and the patients that were not selected for treatment. (B) Survival of the patients that were selected for EBV, selected for LVRC, invited to our hospital for consultation but not selected for BLVR, not selected for BLVR and not invited to our hospital for consultation.

Abbreviations: EBV, endobronchial valve treatment; LVRC, lung volume reduction coil treatment; BLVR, bronchoscopic lung volume reduction; MDT, multidisciplinary team meeting.

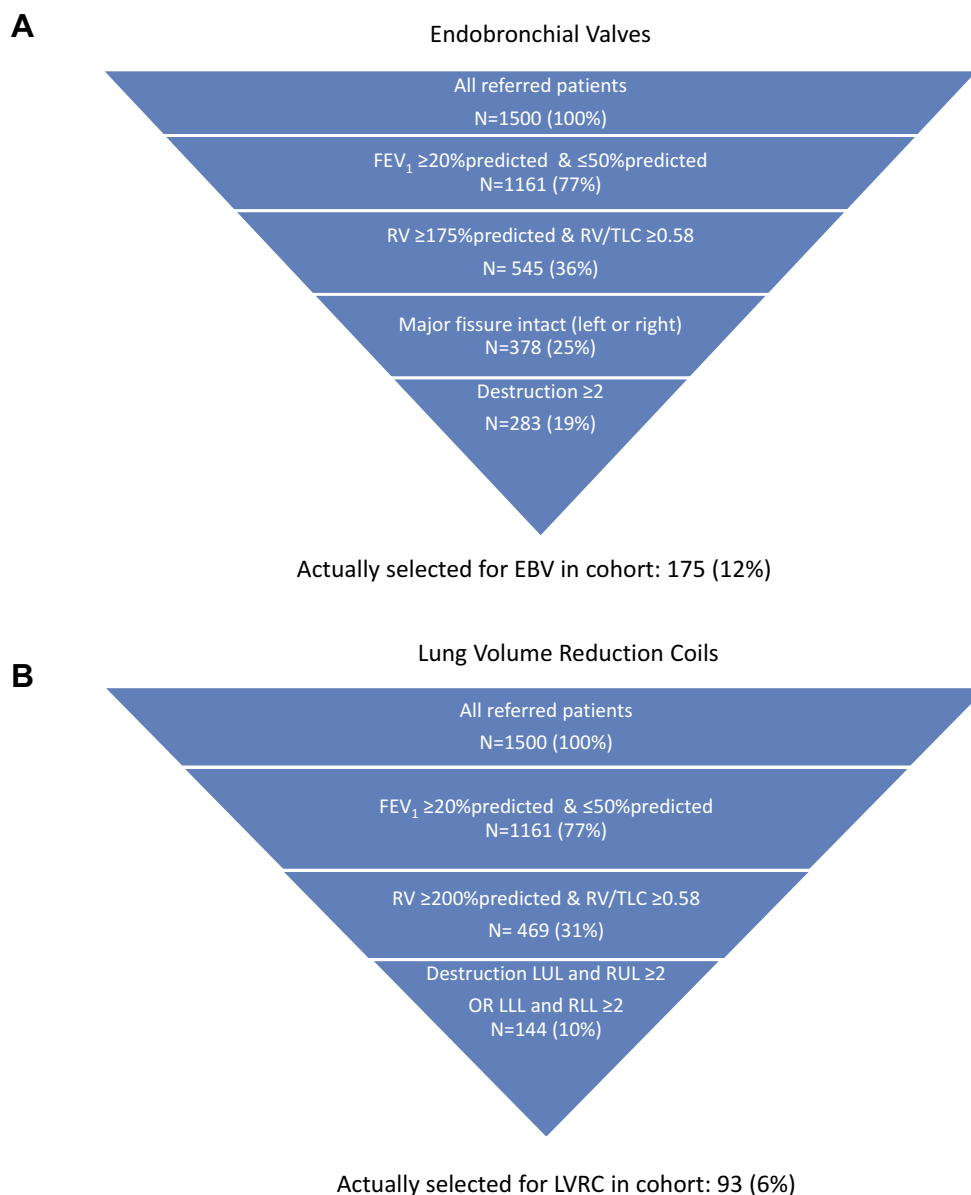


Figure 4 Eligibility for EBV and LVRC after application of current inclusion and exclusion criteria. **(A)** Eligible patients for EBV treatment. **(B)** Eligible patients for LVRC treatment.

Abbreviations: N, number of patients; FEV₁, forced expiratory volume in 1 s; RV, residual volume; TLC, total lung capacity; EBV, endobronchial valve treatment; LUL, left upper lobe; RUL, right upper lobe; LLL, left lower lobe; RLL, right lower lobe; LVRC, lung volume reduction coil treatment.

Ethics and Consent Statement

Given the retrospective and anonymous nature of the analyses, this research did not fall within the scope of the WMO (Dutch Medical Research with Human Subjects Law) and therefore review by a medical ethical committee was not required.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data or analysis and

interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Funding

The University of Groningen, Junior Scientific Masterclass provided financial support for the research position of JW. This analysis was part of the SOLVE project, funded by The Dutch Lung Foundation (Longfonds) (no. 5.1.17.171).

Disclosure

LEGWV reports grants and personal fees from AstraZeneca, personal fees from Novartis, personal fees from GSK, personal fees from Chiesi, personal fees from Menarini, personal fees from Pulmonx, grants from Fisher & Paykel, grants from Philips, personal fees from Boehringer, all outside the submitted work. HAMK reports grants from GSK, grants from Novartis, grants from Boehringer Ingelheim, outside the submitted work. DJS reports grants, personal fees, and non-financial support from PulmonX Inc., CA, USA, grants, personal fees, and non-financial support from PneumRx/BTG, CA, USA, grants and non-financial support from Nuvaira, MN, USA, outside the submitted work. The authors report no other conflicts of interest in this work.

References

- Herth FJF, Slebos D-J, Criner GJ, Valipour A, Sciruba F, Shah PL. Endoscopic lung volume reduction: an expert panel recommendation - update 2019. *Respiration*. 2019;1–10. doi:10.1159/000496122
- van Geffen WH, Slebos D-J, Herth FJ, S V K, Weder W, Shah PL. Surgical and endoscopic interventions that reduce lung volume for emphysema: a systematic review and meta-analysis. *Lancet Respir Med*. 2019;7(4):313–324. doi:10.1016/S2213-2600(18)30431-4
- Klooster K, Ten Hacken NHT, Hartman JE, Kerstjens HAM, van Rikxoort EM, Slebos D-J. Endobronchial valves for emphysema without interlobar collateral ventilation. *N Engl J Med*. 2015;373(24):2325–2335. doi:10.1056/NEJMoa1507807
- Valipour A, Herth FJF, Burghuber OC, et al. Target lobe volume reduction and COPD outcome measures after endobronchial valve therapy. *Eur Respir J*. 2014;43(2):387–396. doi:10.1183/09031936.00133012
- Koster TD, van Rikxoort EM, Huebner R-H, et al. Predicting lung volume reduction after endobronchial valve therapy is maximized using a combination of diagnostic tools. *Respiration*. 2016;92(3):150–157. doi:10.1159/000448849
- Davey C, Zoumot Z, Jordan S, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HiFi study): a randomised controlled trial. *Lancet*. 2015;386(9998):1066–1073. doi:10.1016/S0140-6736(15)60001-0
- Slebos D-J, Cicienia J, Sciruba FC, et al. Predictors of response to endobronchial coil therapy in patients with advanced emphysema. *Chest*. 2019;155(5):928–937. doi:10.1016/j.chest.2019.02.012
- Herth FJF, Eberhardt R, Gompelmann D, et al. Radiological and clinical outcomes of using Chartis™ to plan endobronchial valve treatment. *Eur Respir J*. 2013;41(2):302–308. doi:10.1183/09031936.00015312
- Valipour A, Slebos D-J, Herth F, et al. Endobronchial valve therapy in patients with homogeneous emphysema. Results from the IMPACT Study. *Am J Respir Crit Care Med*. 2016;194(9):1073–1082. doi:10.1164/rccm.201607-1383OC
- Kemp SV, Slebos D-J, Kirk A, et al. A multicenter randomized controlled trial of zephyr endobronchial valve treatment in heterogeneous emphysema (TRANSFORM). *Am J Respir Crit Care Med*. 2017;196(12):1535–1543. doi:10.1164/rccm.201707-1327OC
- Criner GJ, Sue R, Wright S, et al. A multicenter randomized controlled trial of zephyr endobronchial valve treatment in heterogeneous emphysema (LIBERATE). *Am J Respir Crit Care Med*. 2018;198(9):1151–1164. doi:10.1164/rccm.201803-0590OC
- Sciruba FC, Criner GJ, Strange C, et al. Effect of endobronchial coils vs usual care on exercise tolerance in patients with severe emphysema: the RENEW randomized clinical trial. *JAMA*. 2016;315(20):2178–2189. doi:10.1001/jama.2016.6261
- Slebos D-J, Klooster K, Ernst A, Herth FJF, Kerstjens HAM. Bronchoscopic lung volume reduction coil treatment of patients with severe heterogeneous emphysema. *Chest*. 2012;142(3):574–582. doi:10.1378/chest.11-0730
- Deslee G, Klooster K, Hetzel M, et al. Lung volume reduction coil treatment for patients with severe emphysema: a European multicentre trial. *Thorax*. 2014;69(11):980–986. doi:10.1136/thoraxjnl-2014-205221
- Klooster K, Ten Hacken NHT, Franz I, Kerstjens HAM, van Rikxoort EM, Slebos D-J. Lung volume reduction coil treatment in chronic obstructive pulmonary disease patients with homogeneous emphysema: a prospective feasibility trial. *Respiration*. 2014;88(2):116–125. doi:10.1159/000362522
- Come CE, Kramer MR, Dransfield MT, et al. A randomised trial of lung sealant versus medical therapy for advanced emphysema. *Eur Respir J*. 2015;46(3):651–662. doi:10.1183/09031936.00205614
- Slebos D-J, Klooster K, Erasmus M. Emphysema! *Am J Respir Crit Care Med*. 2012;186(2):197. doi:10.1164/rccm.201201-0067IM
- Snell GI, Holsworth L, Khorramnia S, et al. Feasibility and safety of a transthoracic pneumostoma airway bypass in severe emphysema patients. *Respiration*. 2017;93(4):236–246. doi:10.1159/000455878
- Slebos D-J, Shah PL. Collateral ventilation: friend or foe in patients with severe emphysema. *Respiration*. 2017;93(4):232–233. doi:10.1159/000456672
- Shah P, Slebos D-J, Cardoso P, et al. Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial. *Lancet*. 2011;378(9795):997–1005. doi:10.1016/S0140-6736(11)61050-7
- National Emphysema Treatment Trial Research Group, Fishman A, Fessler H, et al. Patients at high risk of death after lung-volume-reduction surgery. *N Engl J Med*. 2001;345(15):1075–1083. doi:10.1056/NEJMoa11798
- Likert R. A technique for the measurement of attitudes. *Arch Psychol*. 1932;22(140):55.
- Polke M, Rötting M, Sarmand N, et al. Interventional therapy in patients with severe emphysema: evaluation of contraindications and their incidence. *Ther Adv Respir Dis*. 2019;13:175346661983549. doi:10.1177/1753466619835494
- Slebos D-J, Breen D, Coad J, et al. safety and histological effect of liquid nitrogen metered spray cryotherapy in the lung. *Am J Respir Crit Care Med*. 2017;196(10):1351–1352. doi:10.1164/rccm.201611-2220LE
- Slebos D-J, Shah PL, Herth FJ, et al. Safety and adverse events after targeted lung denervation for symptomatic moderate to severe COPD (AIRFLOW): a multicenter randomized controlled trial. *Am J Respir Crit Care Med*. 2019;rccm.201903-0624OC. doi:10.1164/rccm.201903-0624OC.
- Tuohy MM, Remund KF, Hilfiker R, Murphy DT, Murray JG, Egan JJ. Endobronchial valve deployment in severe α -1 antitrypsin deficiency emphysema: a case series. *Clin Respir J*. 2013;7(1):45–52. doi:10.1111/j.1752-699X.2012.00280.x
- Hopkinson NS, S V K, Toma TP, et al. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. *Eur Respir J*. 2011;37(6):1346–1351. doi:10.1183/09031936.00100110
- Garner J, S V K, Toma TP, et al. Survival after endobronchial valve placement for emphysema: a 10-year follow-up study. *Am J Respir Crit Care Med*. 2016;194(4):519–521. doi:10.1164/rccm.201604-0852LE
- Gompelmann D, Benjamin N, Bischoff E, et al. Survival after endoscopic valve therapy in patients with severe emphysema. *Respiration*. 2019;97(2):145–152. doi:10.1159/000492274

30. Putcha N, Han MK, Martinez CH, et al. Comorbidities of COPD have a major impact on clinical outcomes, particularly in African Americans. *Chronic Obstr Pulm Dis J COPD Found.* **2014**;1(1):105. doi:10.15326/JCOPDF.1.1.2014.0112
31. Triest FJJ, Franssen FME, Spruit MA, Groenen MTJ, Wouters EFM, Vanfleteren LEGW. Poor agreement between chart-based and objectively identified comorbidities of COPD. *Eur Respir J.* **2015**;46(5):1492–1495. doi:10.1183/13993003.00667-2015
32. Koster TD, Slebos D-J. The fissure: interlobar collateral ventilation and implications for endoscopic therapy in emphysema. *Int J Chron Obstruct Pulmon Dis.* **2016**;11:765–773. doi:10.2147/COPD.S103807
33. Criner GJ, Delage A, Voelker K, et al. Improving lung function in severe heterogenous emphysema with the spiration® valve system (EMPROVE): a multicenter, open-label, randomized, controlled trial. *Am J Respir Crit Care Med.* **2019**:rccm.201902-0383OC. doi:10.1164/rccm.201902-0383OC.
34. Tenda ED, Ridge CA, Shen M, Yang G-Z, Shah PL. Role of quantitative computed tomographic scan analysis in lung volume reduction for emphysema. *Respiration.* **2019**;98(1):1–9. doi:10.1159/000498949
35. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* **2004**;350(10):1005–1012. doi:10.1056/NEJMoa021322
36. Pietzsch JB, Busca R, Rott C, et al. Adoption patterns of bronchoscopic lung volume reduction procedures in germany and predicted procedure volumes for other European countries. *Respiration.* **2019**;97(1):34–41. doi:10.1159/000491677

International Journal of Chronic Obstructive Pulmonary Disease

Dovepress

Publish your work in this journal

The International Journal of COPD is an international, peer-reviewed journal of therapeutics and pharmacology focusing on concise rapid reporting of clinical studies and reviews in COPD. Special focus is given to the pathophysiological processes underlying the disease, intervention programs, patient focused education, and self management

protocols. This journal is indexed on PubMed Central, MedLine and CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-chronic-obstructive-pulmonary-disease-journal>